DATE: Saturday, September 06, 2008 Purge Queries Printable Copy Create Case

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT; PLUR=YES; OP=AND			
L19	L18 and (mab.clm. or monoclonal antibody.clm.)	3	L19
L18	L17 and Tat?.clm.	13	L18
L17	L16 and (mab or monoclonal antibod?)	8264	L17
L16	Tat	19504	L16
L15	L14 and Tat.clm.	1	L15
L14	L13 and Tat	21	L14
L13	cohen david i.in.	650	L13
DB=PGPB; PLUR=YES; OP=AND			
L12	L11 not l4	0	L12
L11	L10 and tolerogen.clm.	2	L11
L10	L9 and (mab.clm. or monoclonal antibody.clm.)	32	L10
L9	L8 and Tat.clm.	82	L9
L8	L7 and (fusion or conjugat?)	2618	L8
L7	L6 and (autoimmun?)	2772	L7
L6	L5 and (Mab or monoclonal antibod?)	7478	L6
L5	Tat	14420	L5
L4	L2 and tolerogen	6	L4
L3	L2 and Tat?.clm.	0	L3
L2	L1 and Tat	61	L2
L1	cohen david i.in.	1950	L1

END OF SEARCH HISTORY

Therapeutic Approaches in Multiple Sclerosis: Lessons from Failed and Interrupted Treatment Trials. Review Article Biodrugs. 16(3):183-200, 2002. *Wiendl, Heinz 1; Hohlfeld, Reinhard 2 3*

Abstract:
The therapy for multiple sclerosis (MS) has changed dramatically over the past decade. Recent immunobiological findings and current pathophysiological concepts together with advances in biotechnology, improvements in clinical trial design and development of magnetic resonance imaging have led to a variety of evaluable therapeutic approaches in MS. However, in contrast to the successfully introduced and established immunomodulatory therapies (e.g. interferon-[beta] and glatiramer acetate), there have been a remarkable number of therapeutic failures as well. Despite convincing immunological concepts, impressive data from animal models and promising results from phase I/II studies, the drugs and strategies investigated showed no benefit or even turned out to have unexpectedly severe adverse effects.

Although to date there is no uniformly accepted model for MS, there is agreement on the significance of inflammatory events mediated by autoreactive T cells in the CNS. These can be modified therapeutically at the individual steps of a hypothetical pathogenetic cascade. Crucial corners like: I. the prevalence and peripheral activation of CNS-autoreactive T cells in the periphery; II. adhesion and penetration of T cells into the CNS; III. local activation and proliferation and; IV. de- and remyelination processes can be targeted through their putative mediators.

Like a 'specificity pyramid', therapeutic approaches therefore cover from general immunosuppression up to specific targeting of T-cell receptor peptide major histocompatibility (MHC) complex.

We discuss in detail clinical MS trials that failed or were discontinued for other reasons. These trials include cytokine modulators [tumour necrosis factor (TNF)-[alpha] antagonists, interleukin-10, interleukin-4, transforming growth factor-[beta]2], immunosuppressive agents (roquinimex, gusperimus, sulfasalazine, cladribine), inducers of remyelination [intravenous immunoglobulins (IVIg)], antigen-derived therapies [oral tolerance, altered peptide ligands (APL), MHC-Peptide blockade], T cell and T-cell receptor directed therapies (T cell vaccination, T-cell receptor peptide vaccination), monoclonal antibodies against leucocyte differentiation molecules (anti-CD3, anti-CD4), and inactivation of circulating T cells (extracorporeal photopheresis).

The main conclusions that can be drawn from these 'negative' experiences are as follows. Theoretically promising agents may paradoxically increase disease activity (lenercept, infliximab), be associated with unforeseen adverse effects (e.g. roquinimex) or short-term favourable trends may reverse with prolonged follow-up (e.g. sulfasalzine). One should not be too enthusiastic about successful trials in animal models (TNF[alpha] blockers; oral tolerance; remyelinating effect of IVIg) nor be irritated by non-scientific media hype (deoxyspergualine; bone marrow transplantation). More selectivity can imply less efficacy (APL, superselective interventions like T-cell receptor vaccination) and antigen-related therapies can stimulate

rather than inhibit encephalitogenic cells. Failed strategies are of high importance for a critical revision of assumed immunopathological mechanisms, their neuroimaging correlates, and for future trial design. Since failed trials add to our growing understanding of multiple sclerosis, 'misses' are nearly as important to the scientific process as the 'hits'.